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Collaborative Review – Prostate Cancer

Testosterone and Prostate Cancer: Revisiting Old Paradigms

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Abstract

Context: Androgens are vital for growth and maintenance of the prostate; however, the notion that pathologic prostate growth, benign or malignant, can be stimulated by androgens is a commonly held belief without scientific basis. Therefore, the current prostatic guidelines for testosterone therapy (TT) appear to be overly restrictive and should be reexamined.

Objective: To review the literature addressing the possible relationship between testosterone and prostate cancer (PCa) and to summarize the main aspects of this issue.

Evidence acquisition: A Medline search was conducted to identify original articles, review articles, and editorials addressing the relationship between testosterone and the risk of PCa development, as well as the impact of TT on PCa development and its natural history in men believed to be cured by surgery or radiation.

Evidence synthesis: Serum androgen levels, within a broad range, are not associated with PCa risk. Conversely, at time of PCa diagnosis, low rather than high serum testosterone levels have been found to be associated with advanced or high-grade disease. The available evidence indicates that TT neither increases the risk of PCa diagnosis nor affects the natural history of PCa in men who have undergone definitive treatment without residual disease. These findings can be explained with the saturation model (which states that prostatic homeostasis is maintained by a relatively low level of androgenic stimulation) and with the observation that exogenous testosterone administration does not significantly increase intraprostatic androgen levels in hypogonadal men. It must, however, be recognized that the literature remains limited regarding the effect of TT on PCa risk. Nonetheless, the current European Association of Urology guidelines state that in hypogonadal men who were successfully treated for PCa, TT can be considered after a prudent interval.

Conclusions: Although no controlled studies have yet been performed and there is a paucity of long-term data, the available literature strongly suggests that TT neither increases the risk of PCa diagnosis in normal men nor causes cancer recurrence in men who were successfully treated for PCa. Large prospective studies addressing the long-term effect of TT are needed to either refute or corroborate these hypotheses.

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1. Introduction

Hypogonadism is a clinical and biochemical syndrome characterized by signs and symptoms of androgen deficiency and low serum testosterone levels. As endogenous testosterone production physiologically declines with increasing age while life expectancy continues to rise, recognition of testosterone deficiency syndrome (TDS) is currently increasing [1]. Recent studies suggest that the annual incidence of TDS in the United States is as high as 500,000 new cases in men aged 40–69 yr [2–4]. Similar estimates were reported in Europe [5] and in Australia [6].

Low serum testosterone levels may be associated with a variety of physical disorders: impaired libido and erectile dysfunction, reduced muscle mass, fat accumulation, cognitive decline, impaired insulin sensitivity, loss of bone mineral density, cardiac morbidity, and a pattern of changes related to the metabolic syndrome [7–11]. Consequently, TDS may have a significant impact on quality of life (QoL).

During the last decade, the potential of testosterone therapy (TT) in alleviating some of these disorders has been established [12–15]. Despite these potential benefits of TT, physicians may be reluctant to recommend it, due to the long-standing fear of either inducing or stimulating prostate cancer (PCa) [16]. These concerns appear to derive from the landmark studies of Huggins and Hodges in 1941 [17,18], which implied a direct correlation between serum testosterone levels and PCa. This translated to a simple principle: Lowering the serum testosterone level would lead to PCa regression, whereas increasing the serum testosterone level would stimulate PCa growth. These findings were supported by subsequent case reports and studies with small sample sizes [19]; thus, most of the current medical guidelines suggest that suspicion of PCa or a previous PCa diagnosis is a relative or clear contraindication for testosterone replacement therapy (TRT) [8,9,20].

Today, almost 70 yr after the landmark studies of Huggins and Hodges, we still follow their first hypothesis, “lowering the serum testosterone level leads to PCa regression,” as the standard of care in patients with metastatic PCa [21]. Recent articles, however, suggest that Huggins and Hodges’ hypothesis that “higher serum testosterone leads to increased PCa risk and invariably stimulates PCa growth” is without much scientific support [22,23]. Several reports, for example, uniformly demonstrated that TT may safely be considered in patients with a history of successfully treated PCa [24–29]. These data raise the question: Is it justifiable to withhold TT, which is known to provide many benefits for symptomatic hypogonadal men, because of a “risk” that is unproven and, in fact, is contradicted by recent reports [30]?

The aim of this review is to identify and to discuss the most relevant articles addressing the relationship between testosterone and PCa. Moreover, we report on the impact of TT on PCa incidence and the putative effect on the natural history of PCa after therapy with curative intent. Finally, current guidelines addressing TT and PCa are introduced and discussed.

2. Evidence acquisition

A Medline search was conducted to identify original articles, review articles, and editorials addressing the relationship between serum levels of androgens and (1) the risk of PCa development, (2) PCa differentiation and tumor stage at diagnosis, and (3) impact of serum androgens on the natural history of PCa after therapy with curative intent. Moreover, we searched articles that addressed the impact of TT on the risk of PCa development and the impact of TT in PCa patients who were treated with curative intent. Key words included *testosterone*, *androgens*, *replacement therapy*, *hypogonadism*, *prostate cancer*, *prostatectomy*, *radiotherapy*, and *brachytherapy*. All of the key words were contained within the Medical Subject Headings (MeSH) database, which represents the controlled vocabulary used for indexing articles for Medline and PubMed. The articles with the highest level of evidence for the various end points examined were identified with the consensus of all of the authors, and they were reviewed.

3. Evidence synthesis

3.1. The effect of testosterone on prostate cancer growth

In men, the majority of testosterone (approximately 90%) is synthesized by the Leydig cells of the testes and an additional roughly 10% is produced in the adrenal glands. Within prostate epithelial cells, testosterone is irreversibly converted into the primary effector androgen, 5 α -dihydrotestosterone (DHT), by the enzyme 5 α -reductase. DHT binds to the cytoplasmatic androgen receptor, and the DHT-androgen receptor complex translocates into the cell nucleus, where it stimulates the transcription of androgen-regulated genes [31].

For physiological development of the prostate, androgens are indispensable; however, several studies suggest that the stimulating effect of testosterone is not indefinite. Fowler and Whitmore reported in 1981 on their experience with testosterone administration to patients with bone metastases from PCa [32]. The authors found that in previously untreated patients, testosterone administration may initially lead to a beneficial response, while in patients with prior orchiectomy or estrogen exposure, testosterone treatment leads to an unfavorable response. The authors concluded that in patients with metastatic PCa, the response to testosterone treatment is largely dependent on the pretreatment serum testosterone level. This theory was expanded by Morgentaler et al, who noted that, beyond a certain serum testosterone concentration, androgens have a limited ability to stimulate PCa growth (Fig. 1) [33]. Further increases in serum testosterone levels do not lead to further prostate stimulation because the binding capacity of the intraprostatic androgen receptors is saturated. Data from binding studies in rat, dog, and human prostate tissues demonstrated that maximal binding of androgen to androgen receptor occurs at 2–3 nM [34–36], which is quite low.

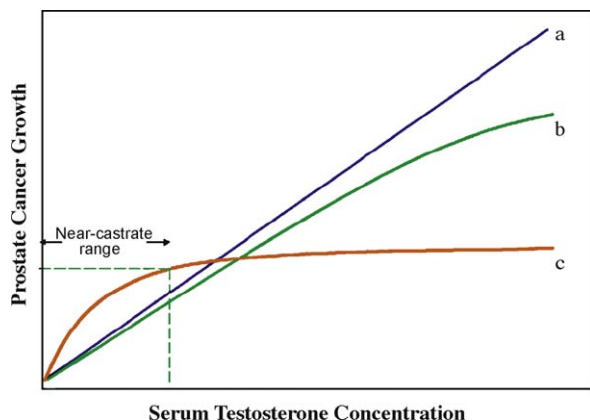


Fig. 1 – The traditional model of testosterone (T)-dependent prostate cancer (PCa) growth suggests that higher serum T concentrations lead to some degree of greater PCa growth (curves a and b). The saturation model (curve c) describes a steep T-dependent curve at T concentrations at or below the near-castrate range, with a plateau representing little or no further growth above this concentration. Reprinted with permission from [33].

This proposed saturation model helps to better explain the conflicting results that were reported in PCa patients who were exposed to exogenous TT. In some of these studies, previously untreated patients as well as orchiectomized patients were included [17,18,32,37]; these two patient populations are entirely different, from the hormonal perspective. Indeed, unfavorable responses to testosterone were predominantly reported in previously castrated patients. Conversely, previously untreated men demonstrated equivocal shifts of the serum acid phosphatase levels or even an increase in the sense of well-being.

Further support for the saturation model comes from studies that assessed the effect of TT on the serum prostate-specific antigen (PSA) level and/or the prostate gland volume. Although TT in hypogonadal men leads to a modest increase in serum PSA level and in prostate volume [38,39], raising serum testosterone to supraphysiologic concentrations in eugonadal men produced no changes in either of these parameters [40,41]. Similarly, in men with low testosterone but not castrate serum levels, TT was found to increase the prostate gland volume, but not beyond the size of age-matched men with eugonadal serum testosterone levels [42].

In this context, a recent case report is also of interest [43]. In this report, a man aged 84 yr with PCa (PSA level: 8.1 ng/ml; Gleason 3+3 histology) and who suffered from symptomatic hypogonadism was treated with TRT for 2 yr. Interestingly, serum PSA levels declined after initiation of TT to a nadir of 5.2 ng/ml, and no clinical progression was reported with follow-up of 21 mo. Undoubtedly, extreme caution should be taken in drawing conclusions from a single-case report, but the finding that TT in a man with untreated, known PCa did not cause obvious progression is very intriguing.

Taken together, the available literature indicates that the stimulating effect of testosterone on the prostate (benign

and malignant tissue) is maximally reached at relatively low serum levels and that a further increase of serum testosterone beyond this saturation point does not lead to additional prostate stimulation.

3.2. The relationship between serum testosterone and prostate cancer incidence

Recently Roddam et al investigated whether circulating sex hormones influence the risk of PCa [23]. They analyzed data from all 19 available published studies in which sex hormones were determined prospectively before PCa diagnosis. A collaborative group was formed among the agreeable investigators (18 of the 19). Overall, data from 3886 PCa patients and 6438 control subjects were pooled, and the relative risk of PCa was calculated by quintile analysis of hormone levels. No statistically significant association was reported between the risk of PCa and the serum concentration of testosterone, of free testosterone, of DHT, of dehydroepiandrosterone sulfate, of androstenedione, of androstenediol glucuronide, of estradiol, or of free estradiol.

Curiously, a number of studies have reported worrisome associations between low serum testosterone and PCa. Morgentaler et al assessed the PCa prevalence in hypogonadal men in two studies [44,45]. In the first study, 77 men with a PSA level <4.0 ng/ml and no suspicious findings on digital rectal examination (DRE) underwent a sextant prostate biopsy. PCa was identified in 14% of the patients. This finding was corroborated in a larger patient cohort ($n = 345$) with similar baseline characteristics in 2006. The overall PCa detection rate (15%) was comparable to that seen in the first study. Additionally, the risk of PCa detection was correlated with the severity of androgen deficiency. In men with a testosterone serum level >250 ng/dl, the PCa rate was 12%; it increased to 21% in men with serum testosterone levels ≤250 ng/dl. In a subset analysis of 184 men, a low testosterone-to-PSA ratio was an independent predictor of PCa after adjustment for age and PSA level [46]. Overall, the reported PCa incidence of these studies is in agreement with the PCa incidence in the placebo arm of the Prostate Cancer Prevention Trial (PCPT) [47], in which 15.2% of the patients with PSA <4.0 ng/ml and a normal DRE were found to harbor PCa in prostate biopsy. The patients in the studies by Morgentaler et al, however, were significantly younger (mean age of 58 yr vs 69 yr). Given that age is an established risk factor for PCa, the PCa incidence may be even higher in an older hypogonadal population.

Additionally, other studies have reported that a low serum testosterone level is associated with advanced pathologic stage, high Gleason score, and biochemical recurrence after radical prostatectomy [48–54]. Nishiyama et al found that in men with high-grade PCa (Gleason score ≥7), the intraprostatic DHT levels were significantly lower compared with men with less aggressive disease (Gleason score ≤6) [55]. Grasso et al reported that at time of PCa diagnosis, the mean serum concentration of sex hormone binding globulin (SHBG; one of the two main serum

testosterone-binding proteins) is significantly higher in PCa patients than in men with benign prostatic enlargement or in healthy individuals [56]. This finding was corroborated in a recent report in which high preoperative SHBG was an independent and highly accurate predictor of lymph node metastasis at radical prostatectomy [57]. Because high levels of SHBG may be associated with low concentrations of bioavailable testosterone, these studies appear to support the counterintuitive concept that low androgen levels may be related to adverse PCa outcomes.

These various studies suggesting a link between low serum testosterone and PCa are provocative, but they cannot be considered conclusive due to methodological issues such as limited population size and retrospective analysis. Moreover, these results are not uniformly observed. Particularly, the large prospective study by Roddam et al failed to identify low testosterone as a risk factor for PCa or to find an association between low testosterone and tumor grade. This discrepancy may be explained by important technical differences. Blood samples, for example, were obtained and frozen several years prior to diagnosis of PCa by Roddam et al, whereas serum testosterone concentrations were obtained concurrently in studies demonstrating a relationship between low testosterone and PCa. Additionally, the study by Roddam et al used different laboratories in different countries and did not directly investigate men with testosterone concentrations in the hypogonadal range.

3.3. Prostate cancer in men receiving testosterone therapy

In 2007, Gooren et al reported that the most frequently cited concern of physicians using TT is that the treatment might induce PCa [16]; however, data assessing the relationship between PCa incidence in men receiving TT are sparse. A few case reports and small retrospective studies have described the development of PCa sometime after TT was initiated [58–60], but prostate biopsies were not performed prior to TT in any of these studies. Because PCa is common in men aged ≥ 50 yr, it is not surprising that some of the men receiving TT were eventually diagnosed with PCa. Therefore, it is unclear whether the reported PCa diagnoses are indeed due to TT or are just coincidence. Moreover, the number of men receiving TT has increased sharply in recent years [61], and the reported number of PCa cases after TT appears to be too small to suggest a clear association.

In 2004, Rhoden and Morgentaler reported on the PCa incidence in seven TT trials, of which three were placebo controlled [62]. PCa was detected in only 5 of the 461 evaluated men (1.1%). Calof et al performed a meta-analysis of 19 double-blinded, randomized, placebo-controlled trials on TT in men ≥ 45 yr [63]. The authors compared the data from 643 men receiving testosterone with data from 427 men receiving placebo. No statistically significantly greater rate of PCa was recorded in testosterone-treated men than in men receiving placebo.

A recently published landmark study further indicates that TT does not exert a deleterious effect on the prostate [38]. Marks et al randomized 44 men with late-onset hypogonadism to either parenteral testosterone or placebo for 6 mo. Twelve-core prostate biopsies were performed prior to randomization to rule out PCa and to assess the prostate tissue levels of testosterone and DHT before TT initiation. Three patients were subsequently excluded from the analysis: one due to treatment related erythrocytosis, one due to a coincident diagnosis of a nonurologic malignancy, and one due to relocation. Some 6 mo after randomization, 40 patients underwent repeat biopsies. Although TT normalized testosterone serum levels (median serum testosterone at baseline: 282 ng/dl vs 640 ng/dl after 6 mo; $p < 0.001$), no significant changes were reported regarding the intraprostatic levels of testosterone or DHT (0.91 ng/dl and 6.79 ng/dl at baseline vs 1.55 ng/dl and 6.82 ng/dl after 6 mo; $p = 0.29$) (Fig. 2). Moreover, the prostate volume was not significantly changed by TT. At repeat biopsy, small PCa foci were found in four men of the placebo group versus two men of the testosterone arm. No treatment-related change was reported in intraprostatic tissue biomarkers for cell proliferation (eg, Ki-67) or in intraprostatic gene expression levels of transcripts encoding known prostate-specific androgen-regulated proteins (eg, PSA).

These findings suggest that the prostatic uptake of circulating androgens is only minimal in men whose serum testosterone levels are restored to normal. Moreover, it supports the previously mentioned saturation theory, emphasizing that at relatively low serum-testosterone levels, intraprostatic androgen levels are sufficient for homeostasis within the organ.

It has been proposed that TT may be harmful in men at increased risk of PCa, such as those with prostatic intraepithelial neoplasia (PIN). This issue was addressed in a study in which hypogonadal patients ($n = 20$) with biopsy-proven PIN received TT for 12 mo [64]. The results were compared with those of patients ($n = 55$) receiving TT for the same time interval without PIN at initial biopsy. No significant differences in PSA responses were noted between these two groups, and in follow-up only a single PCa was detected (in the PIN group).

Finally, testosterone supplementation was demonstrated to suppress tumor growth in PCa xenografts and even to cause reversion from androgen-independent to androgen-dependent phenotypes, both in vivo and in vitro [65–67]. These experimental findings suggest that androgen supplementation may even be beneficial in certain PCa types.

In summary, the available literature does not corroborate the hypothesis that TT is associated with increased PCa risk. Serum androgen levels do not necessarily reflect the intraprostatic androgen levels [36,68], and an increase in serum testosterone within the physiological range is not mirrored by a significant increase of the intraprostatic androgen concentrations. To date, however, the overall number of evaluated patients who received TT is relatively small, and no long-term results are available. Consequently, the long-term effects of TT on prostate carcinogenesis are unclear.

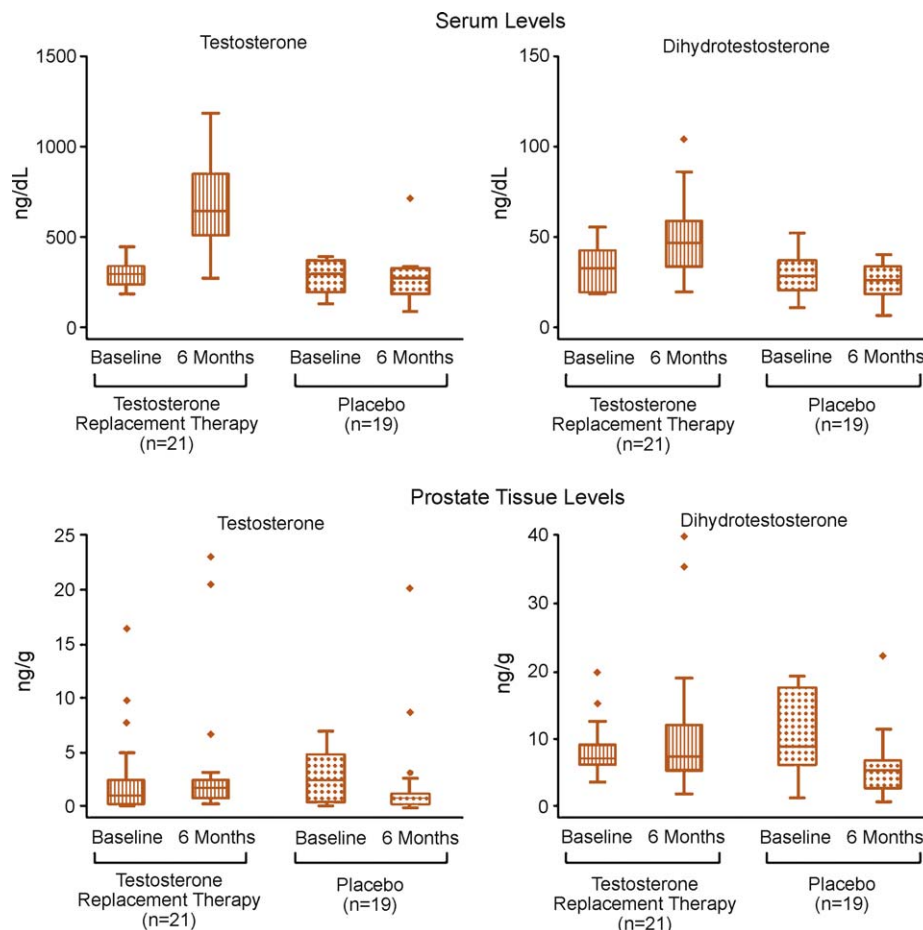


Fig. 2 – The effect of exogenous testosterone (T) administration on the prostate tissue levels of T and dihydrotestosterone (DHT) in hypogonadal men. After 6 mo of T treatment, both T and DHT serum levels significantly increased to the mid- to normal range; however, prostate tissue levels of T and DHT did not change significantly. Reprinted with permission from [38].

3.4. Testosterone therapy after definitive therapy of localized prostate cancer

In the PSA era, the majority of currently diagnosed PCas are localized. Definitive therapy of these tumors with radical prostatectomy, interstitial brachytherapy, or external beam radiotherapy (EBRT) provide a high probability of long-term cancer control or cure. This raises a very practical question: Can TT be considered in a symptomatically hypogonadal man whose PCa has been successfully treated? The rationale for the potential safety of this approach stems from the observation that most men treated definitively are eugonadal before as well as after therapy. Thus, physiologic testosterone levels after therapy with curative intent do not seem to have an adverse effect on cancer control; the majority of these patients are cured.

For several decades TT was clearly contraindicated in patients with previously diagnosed PCa, and few studies address this issue (Table 1); however, virtually all available studies provide similar findings. Five series with a small combined sample size ($n = 74$) have reported on the effect of TT after radical prostatectomy [24,25,27–29]. All patients had a postoperative PSA level <0.1 ng/ml.

Initiation of TT after radical prostatectomy differed substantially in the different series, ranging from immediately after radical prostatectomy to 9 yr postoperatively. Follow-up after TT was 12–24 mo in the majority of the patients. Of the 74 patients reported overall, only 1 (1.4%) experienced biochemical recurrence after TT. This particular patient had a prostatectomy Gleason score of 8, which is an established risk factor for biochemical recurrence.

Compared to radical prostatectomy, the question of TT safety in PCa patients who were treated with interstitial brachytherapy or EBRT is even more intriguing because the prostate remains in situ. Only one study reported on TT after low-dose brachytherapy with or without EBRT [26]. Overall, 36 men received TT in this study, of which 5 men stopped supplementation after 1–3 mo because no beneficial treatment effect was noticed. Median duration of TT in the remaining 31 patients was 4.5 yr. Median follow-up was 5 yr. A transient rise in PSA was reported in one patient. At the last follow-up, 74% of the patients had a PSA value <0.1 ng/ml, and all patients had a PSA value <1 ng/ml. The author concluded that TT may be considered safe after brachytherapy in carefully selected patients.

Table 1 – Reports addressing the effect of testosterone therapy in symptomatic hypogonadal men after definitive prostate cancer treatment

Author	Sample size, <i>n</i>	PCa treatment	Start of TRT after PCa treatment	Follow-up	Cases of BCR
Kaufman and Graydon [29]	7	RP	Mean: 2.7 yr Range: 0–108 mo	Mean: NR Range: 1–12 years	None
Agarwal and Oefelein [28]	10	RP	Not reported	Mean: 19 mo Range: 9–29 mo	None
Khera et al [25]	21	RP	Mean: 54 mo Range: 1–181 mo	Median: 12 mo Range: 1–60 mo	None
Nabulsi et al [27]	22	RP	Mean: 26 mo Range: 2.5–11.8 mo	Mean: 24 mo Range: 14–30 mo	1/22
Davilla et al [24]	20	RP: 14 EBRT: 6	Mean: 74 after RP; 57 mo after EBRT	Mean: 12 mo after RP; 9 mo after EBRT Range: NR	None after RP None after EBRT (according to ASTRO criteria)
Morales et al [69]	5	EBRT	Not reported	Mean 14.6 mo Range: 6–27 mo	None (according to ASTRO criteria)
Sarosdy [26]	31	Brachytherapy (with or without EBRT)	Median: 24 mo Range: 6–54 mo	Median: 60 mo Range: 18–108 mo	None (according to ASTRO criteria) PSA <0.1 in 74% PSA <1.0 in 100%

ASTRO = American Society for Therapeutic Radiation Oncology; BCR = biochemical recurrence; EBRT = external beam radiotherapy; NR = not reported; PCa = prostate cancer; RP = radical prostatectomy; TT = testosterone therapy.

Finally, two studies reported on TT after EBRT [24,69]. In the first report [69], five men with severe hypogonadism were treated with exogenous testosterone after their PSA level reached nadir. The mean follow-up was 14.5 mo (range: 6–27 mo). At the last follow-up, none of the patients had evidence of cancer recurrence, based on PSA levels (according to the American Society for Therapeutic Radiation Oncology [ASTRO] criteria) and DRE. In the second report [24], six men received TT after a mean time of 57 mo after EBRT. Mean follow-up in this series was 9 mo. Again, no biochemical failures according to the ASTRO criteria were recorded.

In summary, the available literature indicates that TT is feasible after curative PCa therapy without jeopardizing cancer control in selected patients who suffer from symptomatic hypogonadism.

3.5. Current guidelines on testosterone therapy

Different guidelines from various medical associations or committees currently exist for the treatment of androgen deficiency [8,9,20]. These guidelines uniformly agree that there is neither evidence that TT increases the risk of developing PCa nor evidence that TT converts subclinical or indolent PCa into clinically significant PCa. Thus, physicians should not be reluctant to recommend TT in symptomatic hypogonadal men out to the fear of inducing PCa. According to one guideline [9], TT is relatively contraindicated in men at high risk of developing PCa, but the guideline does not provide a clear definition of high risk. Moreover, the guidelines likewise state that the literature on TT and PCa is yet too sparse to draw a definite conclusion on the safety of TT with regard to the risk of PCa.

According to all guidelines, TT is contraindicated in men with diagnosed clinical PCa. Therefore, the risk of significant PCa should be assessed with DRE and serum PSA measurement before TT is initiated. In case of suspicious findings

(eg, a palpable nodule), a prostate biopsy should be performed before TT.

The recent European Association of Urology (EAU) guidelines state that TT may be considered in symptomatic hypogonadal men who were successfully treated for PCa, after a prudent interval revealing neither clinical nor laboratory evidence of recurrent disease [9]. However, a *prudent interval* was not defined. The issue of TT after definitive PCa therapy is also addressed in the 2006 guidelines from the Endocrine Society [20]. Due to the paucity of data and the lack of randomized trials, a general recommendation on this topic was not made.

In summary, the recent improvements in the understanding of the relationship between testosterone and PCa are beginning to be partially acknowledged in current guidelines for the treatment of androgen deficiency. In the absence of large-scale studies with long-term follow-up, specific recommendations have not been made regarding the use of TT in men who appear to have been cured of PCa. This lack is understandable because data regarding this issue are only available for 116 men. Although clinicians would benefit from guidelines regarding TT in men with prior history of PCa (ie, the timing of initiation of TT following PCa treatment), the lack of adequate data makes such recommendations impossible at this time.

As indicated above, many men following PCa treatment have normal or even high-normal testosterone levels, and studies have failed to show that these men are at an increased risk of poor outcomes. This said, it is difficult to find arguments that explain why a normal testosterone level that is achieved pharmacologically should be more harmful than a naturally occurring normal testosterone level. Nonetheless, until more data from well-designed studies become available, clinicians must individually discuss the potential risks and benefits of TT before starting therapy. The patient needs to be unambiguously informed about the limited experience in this field, and informed

consent should be especially well documented. Moreover, a thorough follow-up must be guaranteed.

Further aspects of TT guidelines warrant comment. The longstanding prohibition against the use of TT in men with locally advanced or metastatic PCa, for example, seems reasonable, due to the potential for significant deleterious outcomes in such patients [9]. It should also be recognized that early studies of testosterone administration in noncastrated men with metastatic PCa revealed improvement in sense of well-being in many, without evident clinical progression [32,37].

Another question of increasing importance is whether TT is safe or harmful in patients with symptomatic androgen deficiency and diagnosed, untreated, low-grade, localized PCa. Approximately one in seven men (15%) with low testosterone and a PSA level <4 ng/ml has biopsy-detectable, untreated PCa, yet TT trials have not shown any significant increase in PCa rates [44,45,63]. These findings suggest that TT may not even be harmful in men undergoing surveillance for low-risk PCa. Many patients in their 70s or 80s harbor low-risk PCas within the prostate, and some may suffer from symptomatic testosterone deficiency. A substantial proportion of such patients will not receive definitive therapy, due to the concern of overtreatment, yet those with symptomatic hypogonadism may benefit from TT. According to the saturation model, TT should not exert a negative effect on the natural history of PCa in these men, yet traditionally TT has been contraindicated for these men. Moreover, the evidence reviewed in this paper fails to support the historical view that serum testosterone levels in the upper range of normal lead to rapid or aggressive PCa growth. Therefore, appropriate clinical trials designed to clarify any possible relationship between TT and PCa are long overdue [70].

4. Conclusions

Recently published studies have greatly improved our understanding of the interaction between androgens and PCa. The theory that testosterone invariably enhances PCa growth, widely believed for many decades, has not been substantiated. Despite an improved knowledge base, many questions are yet to be answered. Particularly, the long-term effect of exogenous testosterone administration on prostate carcinogenesis and the safety of TT in men with a prior history of PCa remain unknown. Appropriate clinical trials designed to examine the long-term effect of TT on PCa development and natural history after curative therapy should become major priorities in urology.

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Study concept and design: Isbarn, Pinthus, Marks, Montorsi, Morales, Morgentaler, Schulman.

Acquisition of data: Isbarn, Pinthus, Marks, Montorsi, Morales, Morgentaler, Schulman.

Analysis and interpretation of data: Isbarn, Pinthus, Marks, Montorsi,

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Drafting of the manuscript: Isbarn, Pinthus, Marks, Montorsi, Morales, Morgentaler, Schulman.

Critical revision of the manuscript for important intellectual content: Isbarn, Pinthus, Marks, Montorsi, Morales, Morgentaler, Schulman.

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